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THE WEINBERG GROUP INC.

March 10, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: *Citizen Petition 98P-0434/CP1/PSA1*

Dear Sir/Madam:

This letter is in support of the Citizen Petition (98P-0434) filed jointly by Berlex Laboratories, Inc. (Berlex) and 3M Pharmaceuticals, a division of Minnesota Mining & Manufacturing Company. The Citizen Petition requested the Food and Drug Administration (FDA) to establish approval standards for generic transdermal estradiol patches before approving any abbreviated new drug application (ANDA) for a transdermal estradiol patch. The approval standards would assure the bioequivalence of a complex dosage form, a transdermal system intended to maintain therapeutic levels of estradiol for 7-days.

My previous tenure with the FDA, as the Director of the Division of Bioequivalence in the Office of Generic Drugs, and 16 years of FDA experience in regulatory/scientific biopharmaceutics and pharmacokinetics, attest to my expertise in providing my observations and opinions on bioequivalence. In addition, as a practicing pharmacist for nearly 30 years, I have a clinical perspective of the use of generic pharmaceuticals for optimal health care of the American public.

Several weeks ago I obtained the material submitted by Mylan Pharmaceuticals Inc. (Mylan) to the New Jersey Drug Utilization Review Council. This information formed the basis of Mylan's request to include their 7-day estradiol transdermal system (ETS) on New Jersey's List of Interchangeable Drug Products. The material submitted by Mylan included:

- the report of their bioequivalence study
- the request by Bertek, Inc., a subsidiary of Mylan, for a waiver of *in vivo* testing requirements for ETS 0.05 mg/day
- the curriculum vitae of the study investigators
- the statistical analysis of the study

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LET 3

- the *in vitro* data comparing Mylan's ETS to the FDA designated reference listed drug, Berlex's Climara® ETS.

On February 24, 2000, the FDA granted marketing approval to Mylan's ANDAs 75-182 and 75-233 for its ETS 0.1 mg/day and 0.05 mg/day. If, as I believe to be the case, the material, which was submitted to the State of New Jersey, was also the scientific basis for the two ANDAs, I am quite surprised that the FDA has lowered its standards by accepting a poorly designed and inadequate bioequivalence study and has permitted the marketing of Mylan's ETS as bioequivalent to Climara. The FDA's acceptance of the Mylan study for demonstrating bioequivalence to Climara and granting of the waiver for the *in vivo* study of the 0.05 mg/day Mylan ETS is based on unvalidated scientific assumptions. Furthermore, I believe that the FDA has committed a grave injustice to health practitioners and patients using 7-day transdermal estradiol patches as part of their hormone replacement therapy by declaring Mylan's ETS bioequivalent and therefore, substitutable for Climara. My specific comments regarding Mylan's bioequivalence study and why I believe the results do not demonstrate bioequivalence to Climara are detailed below:

FDA SHOULD NOT HAVE ACCEPTED THE MYLAN SUBMISSION

Essential moieties to establish bioequivalence of estradiol

The FDA approval letter indicates August 6, 1997 as the submission date of Mylan's application. The FDA did not follow its policy for accepting an ANDA with a paragraph (iv) certification or, made an error in applying the policy, and the application should not have been accepted until sometime after September 11, 1998 when the analysis of the concentrations of estrone sulfate were completed. At the initial time of submission, it appears that data for estradiol and estrone were in the ANDA. The FDA policy requires, that prior to acceptance of an ANDA, which contains a paragraph (iv) certification, a determination be made that the application is substantially complete and that the included bioequivalence study could establish the bioequivalence of the product.

The FDA has, for at least the last five years, established the specific moieties to be measured in the pharmacokinetic studies of estradiol products. Though no drug specific guidance is available (which is a serious problem the FDA needs to address) as to which moieties to measure, precedent is available from the approval of several ANDAs for estradiol tablets. For the ANDA's estradiol tablets, the FDA has required measuring the concentrations of estradiol, estrone and estrone sulfate. The rationale of the clinical and pharmacokinetic importance for measuring the three aforementioned moieties was clearly described in the Berlex/3M initial Citizen Petition document.

Mylan's protocol (ESTR-9672), dated October 30, 1996, indicated that estradiol and its metabolites, estrone and estrone sulfate would be assayed in the Pharmacokinetics Laboratory of Mylan. However, the study report indicates that samples were assayed for estrone sulfate at Quest Diagnostics Nichols Institute, San Juan Capistrano, CA between

July 29, 1998 and August 21, 1998. If, as it appears from the data I reviewed, the estrone sulfate analysis was not completed until September 11, 1998, the FDA did not have a substantially complete application and the bioequivalence study could not establish bioequivalence of the Mylan ETS to Climara at the time Mylan originally submitted their ANDA.

Multiple dose study for extended-release dosage forms

Mylan apparently only conducted a single dose study of their 0.1 mg/day ETS. At the time of the Mylan submission, the FDA policy and regulation (21 CFR § 320.25 (f)(iii)) required a study at steady-state of a controlled release formulation. The lack of a multiple dose study also should have been grounds for the FDA not to accept the Mylan submission.

In a recently released draft guidance (Guidance for Industry: BA and BE Studies for Orally Administered Drug Products — General Considerations) the FDA does not include a steady-state study as a requirement for ANDAs of extended-release oral dosage forms, which is contrary to its own regulations. Public presentations by senior FDA staffers expressed the extension of this philosophy to transdermal products.

I do not believe that the FDA's position to not require steady-state studies for extended-release dosage forms, especially a 7-day ETS, is based on sound science and introduces a potential lack of efficacy at the end of the dosing interval. As the plasma levels of estradiol, estrone and estrone sulfate decrease during the 7-day period of wear of an ETS, the levels may drop below a minimum effective level. At the time of removal of the old patch and placement of the new patch, there may be several hours before the new patch releases enough drug to reach therapeutic levels. Therefore, a steady-state study would confirm the equivalence of Mylan's ETS to Climara under actual clinical use conditions.

The data from Mylan's study indicates that the plasma levels of all three moieties are lower from Mylan's ETS as compared to Climara, after patch removal. One hour after removal of the patch, mean estradiol plasma concentrations were 58.9 pg/ml after Climara treatment compared to 52.8 pg/ml after Mylan's ETS, a significant difference ($p=0.0115$) even with the high variability. The actual plasma concentrations of the three moieties after patch removal are shown in attached figures 1-3. At the very least, a critical assessment of trough concentrations must be included to demonstrate bioequivalence.

MYLAN'S STUDY DESIGN DOES NOT DEMONSTRATE BIOEQUIVALENCE

Study poorly controlled

Mylan's cross-over study was conducted in thirty-two post-menopausal or surgically sterile female subjects and was open-labeled, randomized, two treatment, three period, single dose and partial replicate design. Subjects were enrolled in three groups,

presumably due to space constraints in the clinical facility. The dates of the study were as follows:

Group A:	Clinical Period 1: December 26, 1996 - January 5, 1997 Clinical Period 2: January 16, 1997 - January 26, 1997 Clinical Period 3: February 6, 1997 - February 16, 1997
Group B:	Clinical Period 1: January 5, 1997 - January 15, 1997 Clinical Period 2: January 26, 1997 - February 5, 1997 Clinical Period 3: February 16, 1997 - February 26, 1997
Group C:	Clinical Period 1: January 9, 1997 - February 19, 1997 Clinical Period 2: January 30, 1997 - February 9, 1997 Clinical Period 3: February 20, 1997 - March 2, 1997

The subjects were housed at the clinical site for only 11 hours before ETS application and then for 24 hours after ETS application. They were then instructed to keep showering to a minimum and avoid baths or soaking altogether.

Not having the subjects housed for the total 7-day study period could have potentially introduced bias. During the different phases of the study, subjects may have been exposed to varying environmental conditions, such as extremes of hot or cold, which are known to contribute significantly to the transdermal penetration of chemicals. Furthermore, the subjects were not instructed to not disturb the ETS during the study period, and subjects may have re-attached systems which appeared to be peeling away from the skin.

After patch removal, the skin site was wiped with two sterile alcohol pads containing 70% isopropyl alcohol. This procedure may have contributed significantly to the plasma concentrations after patch removal, since estradiol delivered from the ETS, but not yet absorbed, would be removed, along with some estradiol containing stratum corneum. As stated above, the analysis of trough concentrations of an extended-release formulation are critical and the alcohol wipe procedure further confounded analysis of end-of-dosing comparison.

Inadequate blood sampling to fully characterize pharmacokinetics

The most critical portion of any pharmacokinetic study is adequate blood sampling to produce an accurate characterization of the pharmacokinetics of the study drug. This becomes highly significant when conducting comparative bioavailability studies, especially for an extended-release dosage form, such as a 7-day ETS.

The blood sampling times in Mylan's study resulted in comparative pharmacokinetic profiles, which are not representative of Climara's performance. After ETS application, blood samples were collected at 6, 12, 18, 24, 48, 72, 96, 120, 144 and 168 hours, prior to

patch removal. This sampling schedule erroneously assumed that by 24 hours absorption from the ETS had plateaued. The pharmacokinetic profile of Climara, as described in several figures in Climara's product labeling, always shows a characteristic peak concentration of estradiol at around 36 hours. Mylan's ETS may also have a similar peak, which may be observed at 36 hours. However, the absence of the 36 hour sampling time, leads to an incorrect conclusion of equivalence between Mylan's ETS and Climara. As can be seen on the attached figures 4-6, interpolating the plasma concentrations from 24 to 48 hours completely missed the true peak concentration and a portion of the area under the curve.

Plasma concentrations much higher than previously observed for Climara

The peak plasma estradiol concentrations of Climara in the Mylan study were 23% higher (and was probably higher if the proper sampling schedule was used as described above) compared to the value reported in the Climara product labeling and the average concentration was 14% higher. This is even more puzzling in view of the Mylan study data reported as baseline adjusted. While cross-study variability in subjects and analytical methodologies may be somewhat explanatory, the higher plasma concentrations in the Mylan study could have occurred from possible taping/overlays to maintain the maximum contact between the ETS and the skin. The adhesion data in the Mylan study also indicate that artificial interventions may have been used to maintain adhesion since not a single Climara, out of 47 applications, was less than 100% attached, and the Mylan ETS had nearly identical perfect adhesion. This could only have occurred if either the patches were secured with tape at initial application or subjects were instructed to apply pressure to the patch when they may have noticed some disattachment.

Safety of subjects

I am very surprised that the Clinical and Pharmacologic Research Institutional Review Board, located at 1052 Maple Drive, Morgantown WV (the same address as the clinical study site) did not find the excessive blood collected from the subjects in this study of concern. Over the 53 day study period, subjects had more than 800 ml of blood collected.

It is well known that many middle aged women are moderately to severely iron deficient, principally due to chronic, menstrual blood loss. Anemia develops extremely late in iron deficiency. It is quite common that a person may have low to absent iron stores, yet still have normal hemoglobin and hematocrit levels. At this time, a relatively small amount of additional blood loss can trigger anemia, and such individuals may not be able to compensate for the 800 ml blood loss during the study. The best way to identify such individuals is with additional hematology testing, in particular serum ferritin. Serum iron and TIBC (total iron binding capacity) also help identify such people. Individuals with deficient iron stores should have been excluded from the study as an additional level of safety. In addition, such subjects should have been identified if they were in the blood

donor pool, and particularly if they, in fact, donated blood (450 ml unit) within the 30 days allowed by the protocol.

Statistical Analysis

The Mylan submission, which I reviewed, contained the statistical analysis of the study. Several issues regarding the statistical analysis raise concerns about the validity of the conclusions of the study.

As described above, the Mylan study was conducted in three groups of subjects at different times. The study report states that the effect of group was tested for statistical significance prior to combining groups and GROUP was not included as a factor in the analysis of variance (ANOVA) model. In my experience, most statisticians I've consulted, have preferred including the GROUP effect in the ANOVA model.

The Mylan study was conducted as a partial replicate design with the randomization of subjects to one of the following four sequences:

1. Climara, Mylan ETS, Mylan ETS
2. Climara, Mylan ETS, Climara
3. Mylan ETS, Climara, Climara
4. Mylan ETS, Climara, Mylan ETS.

The statistical analysis of replicate design studies is not a trivial matter. The analysis in the Mylan submission did not account for the complexity of the replicate design, and the ANOVA model used was the same as used for the traditional two treatment, two period cross over study, but included three periods.

As detailed above, the analysis (bio-analytical and statistical) of plasma estrone sulfate concentrations occurred more than one year after analysis of estradiol and estrone. The statistical model used for the analysis of estrone sulfate was different from that used for the other two moieties and also did not account for the replicate design of the study.

WAIVER OF LOWER STRENGTH LACKS SCIENTIFIC SUPPORT

Mylan requested, and apparently was granted, a waiver from conducting an *in vivo* bioequivalence study of their 0.05 mg/day strength ETS. The support for the waiver was the compositionally proportional components between the high and low strengths, the demonstration of bioequivalence of the 0.1 mg/day strength to Climara and comparative dissolution profiles of the high and low strengths.

Granting of the waiver and allowing the marketing of the 0.05 mg/day product, which was never tested in human subjects, is based on unverified assumptions. Not only is the Mylan ETS an extended-release dosage form intended to release medication for a 7-day period, which in and of itself, should be of greater concern to not grant a waiver, but it is also a transdermal product and involves additional complexities of drug release from the dosage form and transport through skin layers to the systemic circulation. The assumption that the release and absorption process from compositionally proportional products is linear, may not apply to every transdermal product; and, equivalence at a higher strength does not guarantee equivalence at the lower strength.

The *in vitro* test used by Mylan to support their waiver request showed a similar release rate of estradiol for their high and low strengths, but a very different release rate than Climara. The appropriateness of the *in vitro* dissolution test to grant the waiver, and as a product quality dissolution test, is questionable. Mylan's test used a paddle speed of 100 rpm, which is substantially greater then that recommended by the U.S. Pharmacopoeia, or that of other estradiol transdermal system manufacturers.

MYLAN DID NOT DEMONSTRATE EQUIVALENCE WITH ALTERNATE APPLICATION SITE

Climara is approved for application of the system, either on the lower abdomen, or the upper quadrant of the buttock. The Climara product label describes the study conducted to show the comparative bioavailability of the two sites. In my experience, it appears that for estradiol products, plasma estradiol concentrations are higher from application to the buttock as compared to the abdomen. However, this observation is not universal for **every** estradiol product and needs to be verified on a product-by-product basis. Furthermore, Mylan's claim of equivalence when the products were applied to the abdomen may not be valid when the products are applied to the buttock.

Labeling the Mylan ETS identically to Climara and permitting application, either to the buttock or abdomen, is inappropriate. Mylan's claim of equivalence to Climara, at both sites of application, needs to be supported with an *in vivo* study.

INADEQUATE CHARACTERIZATION OF SKIN IRRITATION AND ADHESION

The Federal Register of February 3, 2000 announced the availability of a FDA guidance for the testing of skin irritation and sensitization of generic transdermal drug products. The guidance is dated December, 1999 and provided an acceptable methodology to test that the irritation and adhesion properties of a generic transdermal were not inferior as compared to the innovator product. The data from the Mylan study, while it made an assessment of comparative irritation and adhesion, does not establish anything about the adhesion and irritation characteristics of the Mylan product. The assessments used in the Mylan study fell very short of meeting the requirements described in the FDA guidance. While it may not be reasonable to impose requirements on Mylan (those, which they

were not aware of at the time they initiated the study) it also seems unreasonable for the FDA to permit the marketing of a product, which has not been shown (by the FDA's standards) to have the same, or lower, irritation potential and adhesion properties as Climara. That none of the Climara patches showed any lift, is strongly indicative that artificial means, such as tape overlays, were used to promote adhesion. None of the Climara patches, but two of the Mylan patches, showed significant irritation. This difference is not statistically significant only because the study was so small. On the contrary, whether this difference is clinically significant, should be the subject of an adequately designed follow-up study.

SUMMARY

When I assumed the position as a pharmacokinetic reviewer at the FDA, I went to my supervisor and asked what was the purpose and the focus of reviewing pharmacokinetic submissions. I was told that the principle role of the review was to judge and assure that the objectives of the study were met and the conclusions drawn from the study were substantiated. Further, I was told that we were to consider the data in the submission as accurate (FDA inspectors would verify accuracy of the data) and the main focus of the review was to evaluate the design and conduct of the study as stated in the report.

Mylan's bioequivalence study of their ETS, compared to Climara, had several design and conduct flaws, which impacted the study meeting its objective, i.e., a study to demonstrate bioequivalence, and concluding from the results of the study that Mylan's ETS is bioequivalent to Climara. The main flaws in the study design, as detailed above, were not housing the subjects in the research facility for the entire time of ETS wear, which had the potential of introducing bias and the inadequate blood sampling schedule, resulting in plasma concentration profiles absolutely not representative of Climara.

Very truly yours,

Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

NMF/lby

Enclosures

cc Susan Allen, M.D., FDA, ODE III
Gary Buehler, FDA, OGD
Dale Conner, Pharm.D., FDA, OGD
Florence Houn, M.D., FDA, ODE III
Janet Woodcock, M.D., FDA, CDER

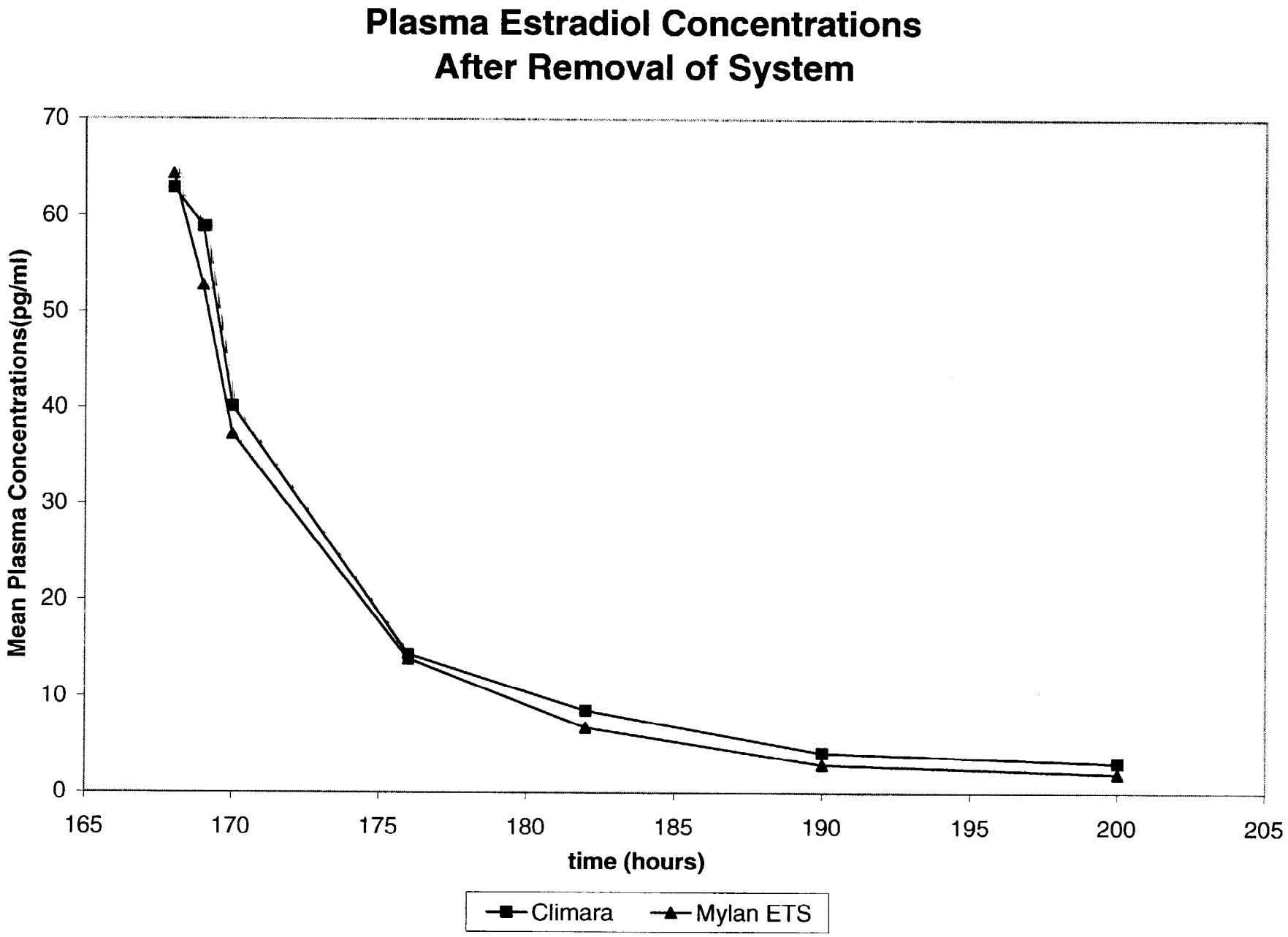

Plasma Estradiol Concentrations
After Removal of System
Mean Plasma Concentrations(pg/ml)
70
60
50
40
30
20
10
0
165
170
175
180
185
190
195
200
205
time (hours)
Climara
Mylan ETS

Figure 1

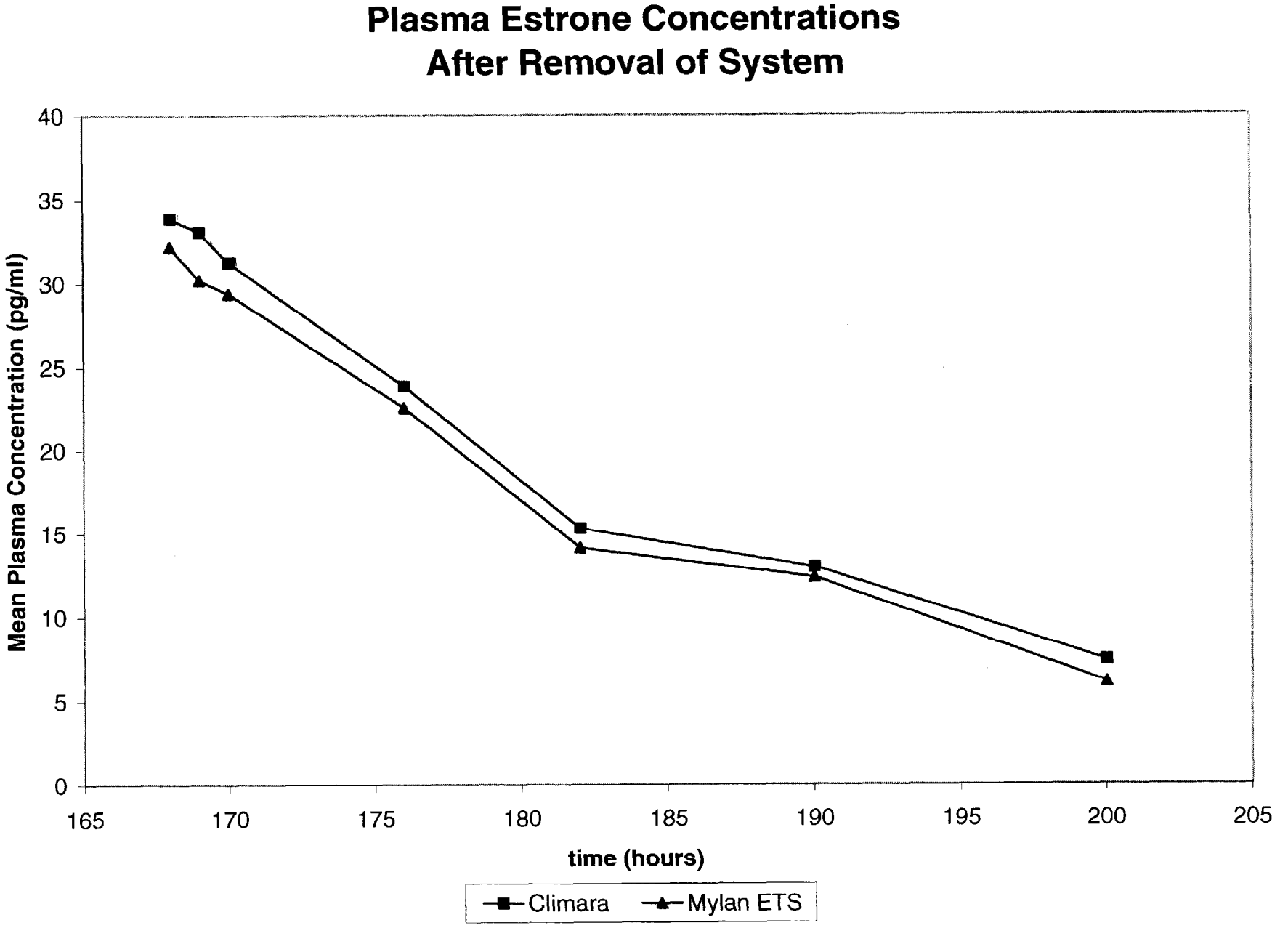
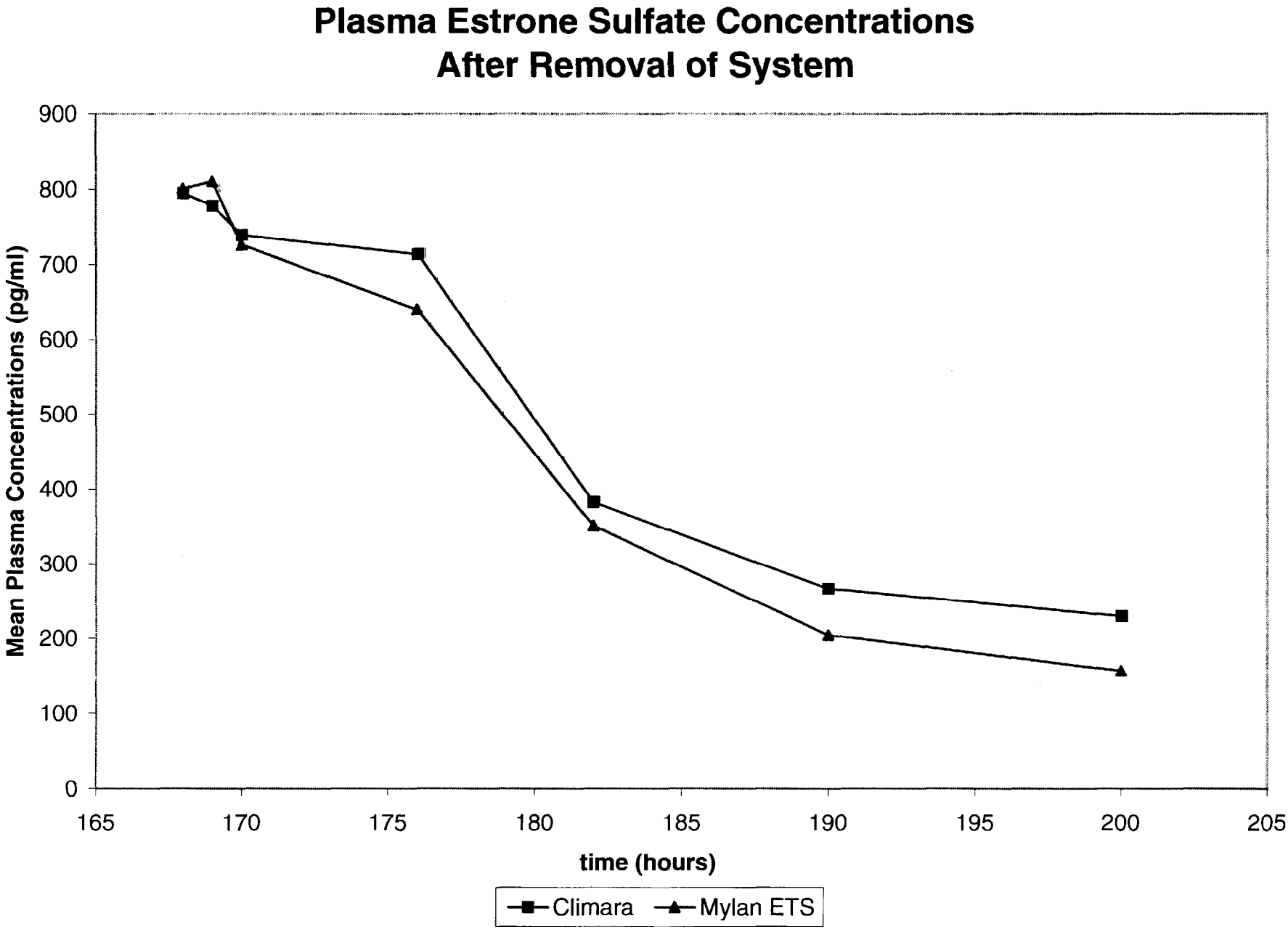

Plasma Estrone Concentrations
After Removal of System
Mean Plasma Concentration (pg/ml)
40
35
30
25
20
15
10
5
0
165
170
175
180
185
190
195
200
205
time (hours)
Climara
Mylan ETS

Figure 2


Plasma Estrone Sulfate Concentrations
After Removal of System
Mean Plasma Concentrations (pg/ml)
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800
700
600
500
400
300
200
100
0
165
170
175
180
185
190
195
200
205
time (hours)
Climara
Mylan ETS

Figure 3

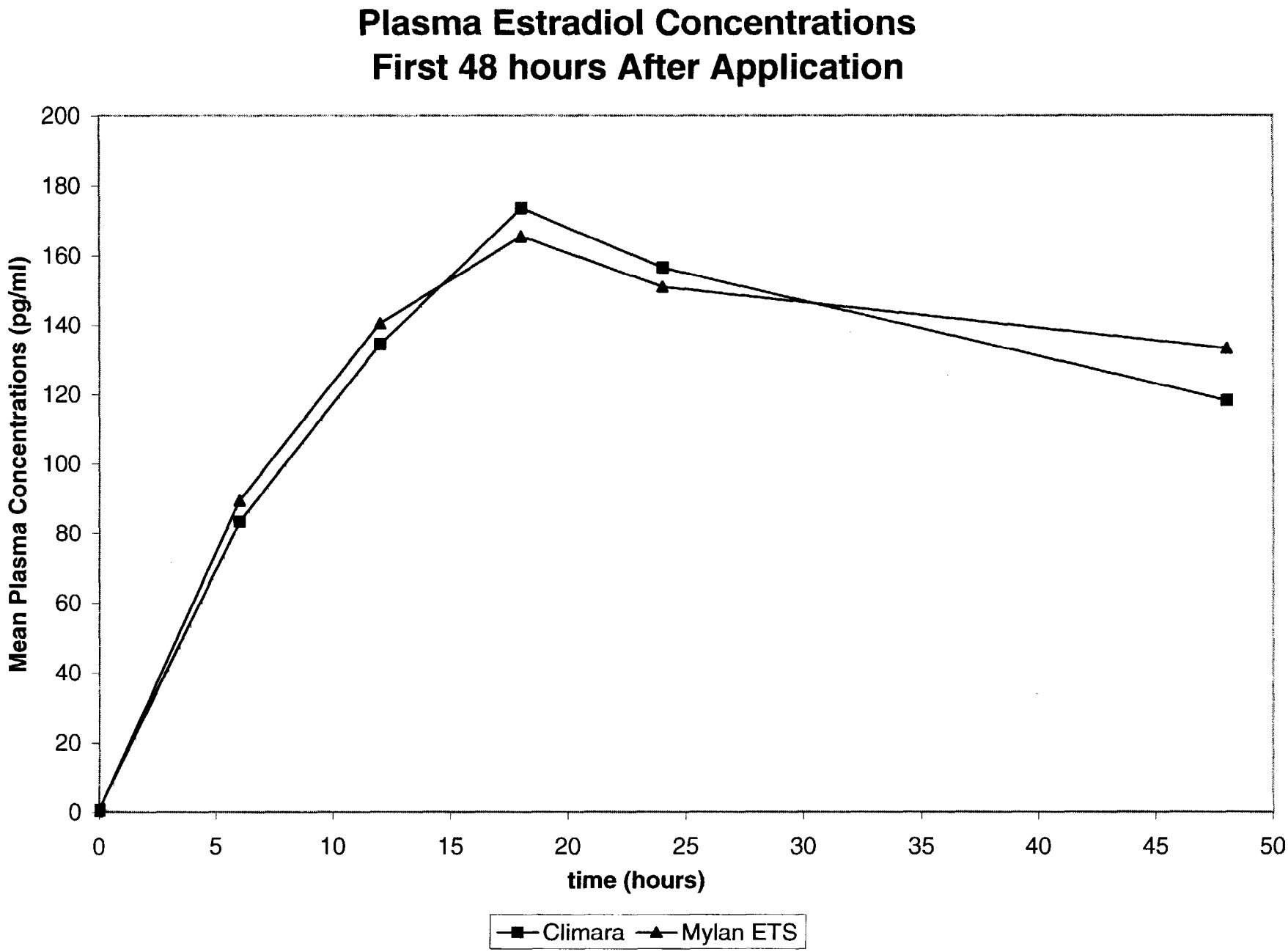
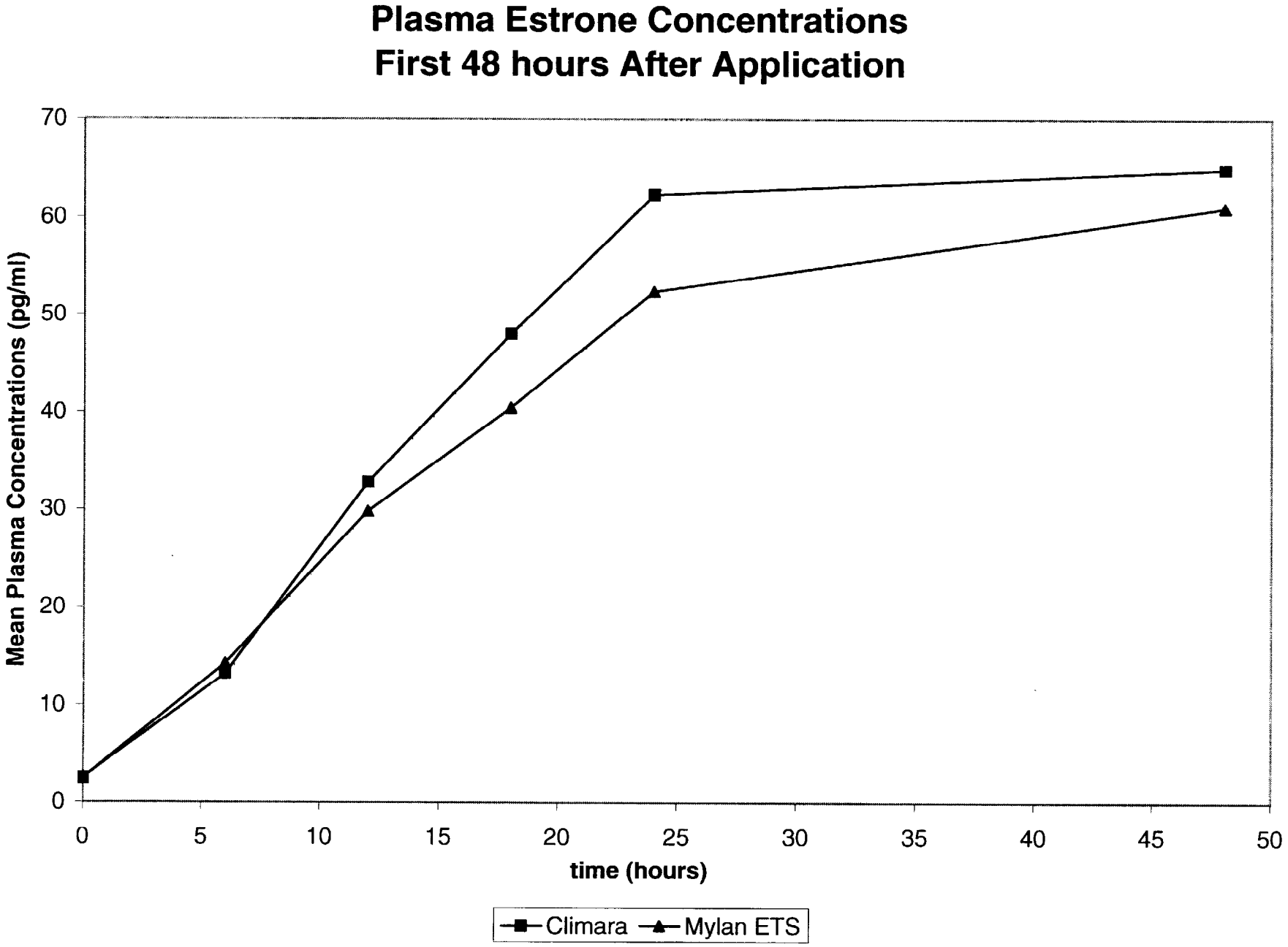

Plasma Estradiol Concentrations
First 48 hours After Application
Mean Plasma Concentrations (pg/ml)
200
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
time (hours)
Climara
Mylan ETS

Figure 4


Plasma Estrone Concentrations
First 48 hours After Application
Mean Plasma Concentrations (pg/ml)
70
60
50
40
30
20
10
0
0
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20
25
30
35
40
45
50
time (hours)
Climara
Mylan ETS

Figure 5

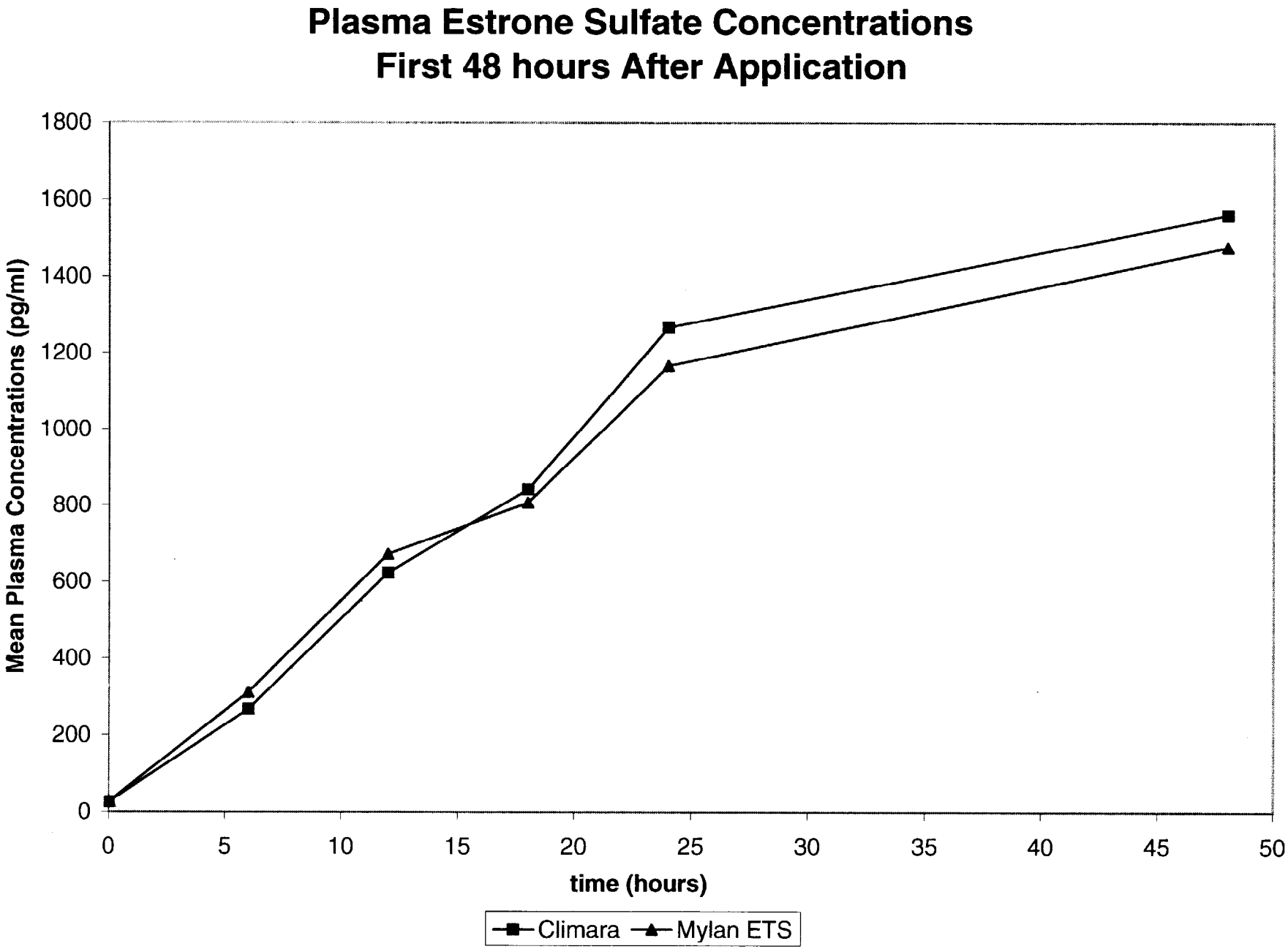
Plasma Estrone Sulfate Concentrations
First 48 hours After Application
Mean Plasma Concentrations (pg/ml)
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
50
time (hours)
Climara
Mylan ETS

Figure 6

331

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4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

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